UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,737	11/25/2003	Bradley S. Galer	BSG 021 US	7300

35812 7590 08/04/2006

GUY DONATIELLO
ENDO PHARMACEUTICALS
100 PAINTERS DRIVE
CHADDS FORD, PA 19317

EXAMINER	
GEORGE, KONATA M	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
IF UNDELIVERABLE RETURN IN TEN DAYS

OFFICIAL BUSINESS

02 1A
0004204479 AUG 04 2006
MAILED FROM ZIP CODE 22314

AN EQUAL OPPORTUNITY EMPLOYER

NOT DELIVERABLE AS ADDRESSED, UNABLE TO FORWARD

NOT DELIVERABLE AS ADDRESSED, UNABLE TO FORWARD

NOT DELIVERABLE AS ADDRESSED, UNABLE TO FORWARD

RECEIVED
AUG 15 2006
USPTO MAIL CENTER

BEST AVAILABLE COPY

Office Action Summary	Application No.	Applicant(s)	
	10/722,737	GALER, BRADLEY S.	
	Examiner	Art Unit	
	Konata M. George	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/30/04;6/21/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 are pending in this application.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on April 30, 2004 was noted and the submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the information disclosure statement, except for the following document: US Patent No. 5,668,830. US Patent No. 5,668,830 is drawn to a "Digital Phase Alignment and Integrated Multichannel Transceiver..." which is not related to the claimed invention.

The information disclosure statement filed June 21, 2004 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Forrest (US 4,963,345) as evidenced by Hawley's Condensed Chemical Dictionary, 1997.

Column 1, lines 63-66 teach the present disclosure is a pharmaceutical, which rapidly reverses or counteracts the effect of the local anesthetic. Hawley's Condensed Chemical Dictionary describes an anesthetic as a chemical compound that induces loss of sensation in a specific part or all of the body. Applicant describes neuropathic negative sensory phenomena as numbness or decreased sensation (spec. paragraph 0002). Therefore, since the prior art teaches a method of reverses or counteracting the effects of a local anesthetic (loss of sensation), then the prior art anticipates claims 1 and 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz et al. (US 5,028,435) in view of Goodman and Gilman's (The Pharmacological Basis of Therapeutics).

Applicant claims a method for treating neuropathic negative sensory phenomena comprising applying an anesthetic to a patient. The anesthetic can be a benzoic acid derivative such as lidocaine, cocaine, etc. and is delivery via a patch.

Determination of the scope and content of the prior art

(MPEP §2141.01)

Katz et al. discloses a system and method for delivery for transdermal drug delivery. The system comprises a matrix layer having a backing or enclosure, wherein the matrix layer contains a drug (col. 2, lines 58-60). Column 5, lines 43-55 teach exemplary drugs which may be delivered by the system of which anesthetics are disclosed (lines 44-45). Figure 1, discloses a system comprising a backing layer and a matrix layer containing the drug (as a solid or liquid) and polymeric beads (col. 11, lines

55-65). Column 5, lines 23-34 teach that the matrix layer can be made from polyvinyl chlorides, silicon rubbers, etc.

Goodman and Gilman's teach examples of local anesthetics such as lidocaine, dibucaine, etc. It is taught that lidocaine can be prepared as an ointment, jelly or topical solution (See Preparations, page 320). It is also taught that market preparations contain 0.5 to 20% and topical mucosal compositions 1 to 5%.

Ascertainment of the difference between the prior art and the claims

(MPEP §2141.02)

The prior art of Katz et al. does not teach the specific anesthetic as claimed by applicant or the weight percent of the drug in the patch.

Finding of prima facie obviousness

***Rational and Motivation* (MPEP §2142-2143)**

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Goodman and Gilman's that lidocaine can be administered topically as an anesthetic in the system of Katz et al. which discloses a transdermal system which can comprise anesthetics to disclose the invention as claimed. Although it is not explicitly disclosed, administering the system near the locus of the negative sensory phenomena would be within the skill of the ordinary worker as part of the process of normal optimization to achieve the desired results of the claimed method.

Telephone Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konata M. George, whose telephone number is 571-272-0613. The examiner can normally be reached from 8AM to 6:30PM Monday to Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter, can be reached at 571-272-0646. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have question on access to the Private Pair system, contact the Electronic Business Center (EBC) as 866-217-9197 (toll-free).

Konata M. George
Patent Examiner
Technology Center 1600

Johann Richter, Ph.D., Esq.
Supervisory Patent Examiner
Technology Center 1600

Notice of References Cited	Application/Control No. 10/722,737	Applicant(s)/Patent Under Reexamination GALER, BRADLEY S.	
	Examiner Konata M. George	Art Unit 1616	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,963,345	10-1990	Forrest, Kim K.	514/248
*	B	US-5,028,435	07-1991	Katz et al.	424/484
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Lewis, Jr., Richard, Hawley's Condensed Chemical Dictionary, 1997, John Wiley & Sons, Inc., 13th Edition, page 75
	V	Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 1990, Pergamon Press, 8th Edition, pages 320-321.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08A (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/722,737
Filing Date	November 25, 2003
First Named Inventor	Bradley S. Galer et al
Art Unit	1616
Examiner Name	
Attorney Docket Number	BSG 021 US

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
KG		US- 2003/0124174 A1	07-03-2003	Galer	
		US- 2002/0049229 A1	04-25-2002	Yamamoto et al	
		US- 2002/0040025 A1	04-04-2002	Hogenkamp et al.	
		US- 2002/0037926 A1	03-28-2002	Lan	
		US- 6,355,637 B1	03-12-2002	Axt et al.	
		US- 6,337,423 B1	01-08-2002	Axt et al.	
		US- 6,248,788 B1	06-19-2001	Robbins et al.	
		US- 6,166,085	12-26-2000	Chaplan et al.	
		US- 6,147,102	11-14-2000	Borgman	
		US- 5,985,933	11-16-1999	Zeitlin	
		US- 5,976,547	11-02-1999	Archer et al.	
		US- 5,885,597	03-23-1999	Botknecht et al.	
		US- 5,866,157	02-02-1999	Higo et al.	
		US- 5,849,737	12-15-1998	Chaplan et al	
		US- 5,776,952	07-07-1998	Liedtke	
		US- 5,741,510	04-21-1998	Rolf et al.	
		US- 5,709,869	01-20-1998	Hind	
~~KG~~	~~—~~	~~US- 5,668,830~~	~~11-18-1997~~	~~Berger et al~~	~~—~~
KG		US- 5,411,738	05-02-1995	Hind	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	KAMC	Date Considered	5.16.06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08A (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/722,737
Filing Date	November 25, 2003
First Named Inventor	Bradley S. Galer et al
Art Unit	1616
Examiner Name	
Attorney Docket Number	BSG 021 US

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
KC		US- 5,589,180	12-31-1996	Hind	
KC		US- 5,536,263	07-16-1996	Rolf et al	
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	KM	Date Considered	5.16.06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

GOODMAN and GILMAN's

The Pharmacological Basis of Therapeutics

EIGHTH EDITION

PERGAMON PRESS
Member of Maxwell Macmillan Pergamon Publishing Corporation
New York • Oxford • Beijing • Frankfurt • São Paulo • Sydney • Tokyo • Toronto

CNS. The symptoms and treatment of poisoning and the misuse of cocaine are discussed in Chapter 22.

Preparations and Dosage. *Cocaine* and *cocaine hydrochloride* are the official preparations of the alkaloid. Cocaine is not prepared legitimately to be used internally or injected. Solutions used clinically for surface anesthesia usually vary from 1 to 4%, depending on the mucosa being anesthetized. Cocaine and epinephrine or other sympathomimetics should not be used concurrently.

Cocaine is included among the drugs controlled by the federal drug-abuse regulations (*see* Appendix I).

LIDOCAINE

Lidocaine, introduced in 1948, is now the most widely used local anesthetic. Its chemical structure is shown in Table 15–1.

Pharmacological Actions. The pharmacological actions that lidocaine shares with other local anesthetic drugs have been presented. Lidocaine produces more prompt, more intense, longer-lasting, and more extensive anesthesia than does an equal concentration of procaine. Unlike procaine it is an aminoethylamide. It is an agent of choice, therefore, in individuals sensitive to ester-type local anesthetics.

Absorption, Fate, and Excretion. Lidocaine is relatively quickly absorbed after parenteral administration and from the gastrointestinal tract. Although it is effective when used without any vasoconstrictor, in the presence of epinephrine the rate of absorption and the toxicity are decreased and the duration of action is prolonged. Lidocaine is dealkylated in the liver by mixed-function oxidases to monoethylglycine xylidide and glycine xylidide, which can be metabolized further to monoethylglycine and xylidide. Both monoethylglycine xylidide and glycine xylidide retain local anesthetic activity. In man about 75% of xylidide is excreted in the urine as the further metabolite 4-hydroxy-2,6-dimethylaniline (*see* Arthur, 1987).

Toxicity. Overdosage of lidocaine produces death from ventricular fibrillation or, if massive, cardiac arrest; procaine, on the other hand, tends to depress respiration rather than the circulation. Side effects of lidocaine are related to its CNS effects and include sleepiness, dizziness, paresthesias, altered mental status, coma, and seizures. The metabolites monoethylglycine xylidide and glycine xylidide may contribute to some of these side effects.

Preparations. *Lidocaine hydrochloride* (*lignocaine;* XYLOCAINE, others) is very soluble in water and alcohol. Preparations include injections, ointments, jelly, topical solutions, and topical aerosol for oral mucosa. Market preparations (0.5 to 20%), some with and without epinephrine (1:50,000 to 1:200,000), are suitable for infiltration (0.5 to 1% block (1 to 2%), and topical mucosal anesthesia (1 to 5%).

Clinical Uses. Lidocaine has a variety of clinical uses as a local anesthetic. In addition, lidocaine is employed as an antiarrhythmic agent, as described in Chapter 35.

OTHER SYNTHETIC LOCAL ANESTHETICS

The number of synthetic local anesthetics is so large that it is impractical to consider all of them here.

Some local anesthetic agents are too toxic to be given by injection. Their use is restricted to topical application to the eye, the mucous membranes, or the skin. Many local anesthetics are suitable, however, for infiltration or injection to produce nerve block; some of them are also useful for topical application. The main categories of local anesthetics are given below; the agents are listed alphabetically.

LOCAL ANESTHETICS SUITABLE FOR INJECTION

Bupivacaine hydrochloride (MARCAINE, SENSORCAINE) is a widely used amide type of local anesthetic; its structure is identical to that of mepivacaine except that a butyl group replaces the methyl substituent on the amino nitrogen. It is a potent agent capable of producing prolonged anesthesia. Its mean duration of action is greater than that of tetracaine, while the toxicity of the two compounds is similar. As with other highly potent local anesthetics (such as tetracaine and etidocaine), bupivacaine can cause a variety of cardiac toxicities. In relatively low concentrations it slows conduction in various regions of the heart, and it may depress cardiac contractility (Covino, 1987). Recovery is relatively slow (*see* Courtney and Strichartz, 1987). Bupivacaine hydrochloride is available in solutions for injection (0.25, 0.5, and 0.75%) with or without epinephrine (1:200,000). The 0.75% solution should not be used for obstetrical anesthesia. A hyperbaric solution for spinal anesthesia is also available.

Chloroprocaine hydrochloride (NESACAINE) is a halogenated derivative of procaine, the pharmacological properties of which it shares almost completely. Its anesthetic potency is at least twice as great as that of procaine, and its toxicity is lower because of its more rapid metabolism. Questions have been raised about the possibility of neurological toxicity from the use of chloroprocaine in spinal anesthesia (*see* Covino, 1987). Some authors have attributed this toxicity to the presence of bisulfite as an antioxidant in the anesthetic solution (see Covino, 1987; however, *see also* Kalichman et al., 1988). Chloroprocaine hydrochloride is available in solutions for injection (1.0, 2.0, and 3.0%).

Etidocaine hydrochloride (DURANEST) is a long-acting derivative of lidocaine. The time required for induction of anesthesia with etidocaine is about the same as that for lidocaine, but its analgesic action lasts two to three times longer. It is

for spinal anesthesia, but is useful fc
for all types of infiltration and regio
Etidocaine hydrochloride is market
for injection (1.0%) with or witho
(1:200,000) and in a 1.5% solution wi
(1:200,000).

Mepivacaine hydrochloride (CAR
ers) is a local anesthetic of the an
Table 15–1). Its pharmacological
similar to those of lidocaine, whic
chemically. Its action is more rapi
somewhat more prolonged than that
has been employed for all types of
regional nerve block anesthesia. M
drochloride is marketed in solution
(1.0, 1.5, 2.0, and 3.0% without,
levonordefrin as a vasoconstrictor).

Prilocaine hydrochloride (CITANE
anesthetic of the amide type. Its pl
properties resemble those of lidoc
and duration of action are longer tha
caine. Like lidocaine, it may produc
unique toxic aftereffect is methe
which is caused by its metabolites.
largely confined to dental procedu
hydrochloride is marketed in a solu
tion (4% with or without epinephrir

Procaine hydrochloride (NOVOCA
used widely; it has largely been dis
caine and its congeners. Procaine (*s*
is hydrolyzed *in vivo* to produce par
acid, which inhibits the action of
This fact is occasionally of practic
Procaine is rapidly absorbed follov
administration; vasoconstrictors ma
procaine solutions to prolong its ac
usually contain 0.25 to 0.5% proca
tion anesthesia, 0.5 to 2% for pe
block, and 10% for spinal anesthes
largely ineffective when applied to
Tetracaine hydrochloride (PONTO
rivative of paraaminobenzoic acid (*s*
It is about ten times more toxic a
than procaine after intravenous inje
cal anesthesia of the eye, a 0.5% s
ment is used; for the mucous me
nose and throat, a 2.0% solution. F
thesia, a total dose of 5 to 20 mg is
effects are longer lasting than tho
Tetracaine hydrochloride for inject
in solutions and in ampuls containi
An ointment (0.5%) and cream (1
application to skin are also availab

LOCAL ANESTHETICS LARGELY RE TO OPHTHALMOLOGICAL USE

While certain of the agents descr
be used in the eye, the following l
agents are largely restricted to the
corneal anesthesia. Their main adv
prototype, cocaine, is that they pro
mydriasis or corneal injury.

Benoxinate hydrochloride is a be
related to procaine. A single instil

: suitable for infiltration (0.5 to 1%),
), and topical mucosal anesthesia (1

. Lidocaine has a variety of clinical
anesthetic. In addition, lidocaine is
n antiarrhythmic agent, as described

THETIC LOCAL
'S

r of synthetic local anesthetics is so
; impractical to consider all of them

anesthetic agents are too toxic to be
tion. Their use is restricted to topical
the eye, the mucous membranes, or
y local anesthetics are suitable, how-
tration or injection to produce nerve
of them are also useful for topical ap-
e main categories of local anesthetics
low; the agents are listed alphabeti-

THETICS SUITABLE FOR INJECTION

ne hydrochloride (MARCAINE, SENSOR-
videly used amide type of local anes-
ucture is identical to that of mepiva-
that a butyl group replaces the methyl
on the amino nitrogen. It is a potent
e of producing prolonged anesthesia.
ration of action is greater than that
, while the toxicity of the two com-
milar. As with other highly potent lo-
ics (such as tetracaine and etidocaine),
can cause a variety of cardiac toxic-
tively low concentrations it slows con-
arious regions of the heart, and it may
diac contractility (Covino, 1987). Re-
relatively slow (*see* Courtney and
1987). Bupivacaine hydrochloride is
solutions for injection (0.25, 0.5, and
1 or without epinephrine (1:200,000).
solution should not be used for obstetri-
sia. A hyperbaric solution for spinal
is also available.
ocaine hydrochloride (NESACAINE) is a
l derivative of procaine, the pharmaco-
perties of which it shares almost com-
anesthetic potency is at least twice as
at of procaine, and its toxicity is lower
its more rapid metabolism. Questions
raised about the possibility of neurologi-
from the use of chloroprocaine in spinal
(*see* Covino, 1987). Some authors have
this toxicity to the presence of bisulfite
oxidant in the anesthetic solution (*see*
'87; however, *see also* Kalichman *et al.*,
proprocaine hydrochloride is available in
or injection (1.0, 2.0, and 3.0%).
ne hydrochloride (DURANEST) is a long-
vative of lidocaine. The time required for
of anesthesia with etidocaine is about the
nat for lidocaine, but its analgesic action

lasts two to three times longer. It is not employed for spinal anesthesia, but is useful for epidural and for all types of infiltration and regional anesthesia. Etidocaine hydrochloride is marketed in solutions for injection (1.0%) with or without epinephrine (1:200,000) and in a 1.5% solution with epinephrine (1:200,000).

Mepivacaine hydrochloride (CARBOCAINE, others) is a local anesthetic of the amide type (*see* Table 15–1). Its pharmacological properties are similar to those of lidocaine, which it resembles chemically. Its action is more rapid in onset and somewhat more prolonged than that of lidocaine. It has been employed for all types of infiltration and regional nerve block anesthesia. Mepivacaine hydrochloride is marketed in solutions for injection (1.0, 1.5, 2.0, and 3.0% without, and 2% with, levonordefrin as a vasoconstrictor).

Prilocaine hydrochloride (CITANEST) is a local anesthetic of the amide type. Its pharmacological properties resemble those of lidocaine. Its onset and duration of action are longer than those of lidocaine. Like lidocaine, it may produce sleepiness. A unique toxic aftereffect is methemoglobinemia, which is caused by its metabolites. Its use is now largely confined to dental procedures. Prilocaine hydrochloride is marketed in a solution for injection (4% with or without epinephrine).

Procaine hydrochloride (NOVOCAIN) was once used widely; it has largely been displaced by lidocaine and its congeners. Procaine (*see* Table 15–1) is hydrolyzed *in vivo* to produce paraaminobenzoic acid, which inhibits the action of sulfonamides. This fact is occasionally of practical significance. Procaine is rapidly absorbed following parenteral administration; vasoconstrictors may be added to procaine solutions to prolong its action. Solutions usually contain 0.25 to 0.5% procaine for infiltration anesthesia, 0.5 to 2% for peripheral nerve block, and 10% for spinal anesthesia. Procaine is largely ineffective when applied topically.

Tetracaine hydrochloride (PONTOCAINE) is a derivative of paraaminobenzoic acid (*see* Table 15–1). It is about ten times more toxic and more active than procaine after intravenous injection. For topical anesthesia of the eye, a 0.5% solution or ointment is used; for the mucous membranes of the nose and throat, a 2.0% solution. For spinal anesthesia, a total dose of 5 to 20 mg is adequate. The effects are longer lasting than those of procaine. Tetracaine hydrochloride for injection is available in solutions and in ampuls containing the dry salt. An ointment (0.5%) and cream (1%) for topical application to skin are also available.

LOCAL ANESTHETICS LARGELY RESTRICTED TO OPHTHALMOLOGICAL USE

While certain of the agents described above can be used in the eye, the following local anesthetic agents are largely restricted to the production of corneal anesthesia. Their main advantage over the prototype, cocaine, is that they produce little or no mydriasis or corneal injury.

Benoxinate hydrochloride is a benzoic acid ester related to procaine. A single instillation of 1 or 2 drops of a 0.4% solution produces within 60 seconds a sufficient degree of anesthesia to permit Schiötz tonometry. It is marketed as a 0.4% ophthalmic solution in combination with 0.25% fluorescein.

Proparacaine hydrochloride (ALCAINE, OPHTHAINE, others) is a benzoate ester, but it is chemically distinct from procaine, benoxinate, and tetracaine. This difference in chemical structure may explain the lack of cross-sensitization between proparacaine and other local anesthetic agents. It is about as potent as tetracaine. Unlike some topical anesthetics, proparacaine hydrochloride produces little or no initial irritation. It is available in a 0.5% ophthalmic solution for topical application.

LOCAL ANESTHETICS USED MAINLY TO ANESTHETIZE MUCOUS MEMBRANES AND SKIN

Some anesthetics are either too irritating or too ineffective to be applied to the eye. However, they are useful as topical anesthetic agents on the skin and/or mucous membranes. These preparations are effective in the symptomatic relief of anal and genital pruritus, poison ivy rashes, and numerous other acute and chronic dermatoses.

Dibucaine (*cinchocaine*, NUPERCAINAL) is a quinoline derivative. Its toxicity resulted in its removal from the United States market as an injectable preparation. It is currently available as a cream and an ointment for use on the skin.

Dyclonine hydrochloride (DYCLONE) has a rapid onset of action and a duration of effect comparable to that of procaine. It is absorbed through the skin and mucous membranes. The compound is used as a 0.5 or 1.0% solution for topical anesthesia in otolaryngology and for anogenital anesthesia.

Pramoxine hydrochloride (TRONOTHANE, others) is a surface anesthetic agent that is not of the benzoate ester type. Its distinct chemical structure is likely to minimize the danger of cross-sensitivity reactions in patients allergic to other local anesthetics. Pramoxine produces satisfactory surface anesthesia and is reasonably well tolerated on the skin and mucous membranes. It is too irritating to be used on the eye or in the nose. Preparations available for topical application include a 1% cream or lotion.

ANESTHETICS OF LOW SOLUBILITY

Some local anesthetics are poorly soluble in water and, consequently, too slowly absorbed to be toxic. They can be applied directly to wounds and ulcerated surfaces, where they remain localized for long periods of time to produce a sustained anesthetic action. Chemically, they are esters of paraaminobenzoic acid that lack the terminal amino group possessed by the previously described local anesthetics. The most important member of the series is *benzocaine* (*ethyl aminobenzoate*; AMERICAINE ANESTHETIC, others). Benzocaine is identical to procaine structurally, except that it lacks the terminal diethylamino group. It is incorporated into a large number of topical preparations.

Hawley's

Condensed Chemical

Dictionary

THIRTEENTH EDITION

Revised by

Richard J. Lewis, Sr.

JOHN WILEY & SONS, INC.
New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

catalyst to form hydrogen cyanide. Side reactions are hydration of methane to carbon dioxide and hydrogen, and oxidation of methane and ammonia to carbon monoxide and nitrogen. The reaction is strongly exothermic. The process has been elaborated wherever natural gas is abundant.

anesthetic. A chemical compound that induces loss of sensation in a specific part or all of the body. A brief classification of the more important agents is as follows:

(A) General
  (1) Hydrocarbons
    (a) Cyclopropane (USP). Effective in presence of substantial proportions of oxygen; flammable.
    (b) Ethylene (USP). Rapid anesthesia and rapid recovery; flammable.
  (2) Halogenated hydrocarbons
    (a) Chloroform. Nonflammable. Its use is being abandoned because of its high toxicity.
    (b) Ethyl chloride. A gas at room temperature, liquefies at relatively low pressure. Applied as a stream from container directly on tissue. Sometimes used in gaseous form as inhalation-type general anesthetic. Flammable.
    (c) Trichloroethylene. Toxic and flammable. Used as general anesthetic since 1934.
  (3) Ethers
    (a) Ethyl ether (USP). First anesthetic used in surgery (1846), now largely replaced with less dangerous types. Highly flammable; explodes in presence of spark or open flame.
    (b) Vinyl ether. A liquid having many of the physiological properties of ethylene and ethyl ether. Highly flammable.
  (4) Miscellaneous
    (a) Tribromoethanol. Basal anesthetic, supplemented by an inhalation type when general anesthesia is needed. Ingredient of "Avertin."
    (b) Nitrous oxide. Originally prepared by Priestley in 1772 (laughing gas); first used as anesthetic by Humphry Davy in 1800. Used (with oxygen) largely for dental surgery. Nonflammable.
    (c) Barbiturates.

(B) Local
  (1) Alkaloids (cocaine)
  (2) Synthetic products (procaine group, e.g., "Novocain"); alkyl esters of aromatic acids (topical).
  (3) Quinine hydrochloride.

anethole. (anise camphor; *p*-methoxypropenylbenzene; *p*-propenylanisole). $CH_3CH{:}CHC_6H_4OCH_3$.
Properties: White crystals; sweet taste; odor of oil of anise. Affected by light. D 0.983–0.987, refr index 1.557–1.561, optical rotation 0.08, mp 22–23C, distillation range 234–237C. Soluble in 8 volumes of 80% alcohol, 1 volume of 90% alcohol; almost immiscible with water.
Derivation: By crystallization from anise or fennel oils; synthetically from *p*-cresol.
Grade: USP, technical, FCC.
Use: Perfumes, particularly for dentifrices, flavors, synthesis of anisic aldehyde, licorice candies, color photography (sensitizer in color-bleaching process), microscopy.

Anfinsen, Christian B. (1916–). An American biochemist who won the Nobel prize for chemistry in 1972. His work involved the molecular basis of evolution and the chemistry of enzymes. He worked with Moore and Stein. His doctorate was granted from Harvard.

ANFO. A high explosive based on ammonium nitrate.
See explosive, high.

angelic acid. (*cis*-2-methyl-2-butenoic acid; α-methyl-crotonic acid). $CH_3CH{:}C(CH_3)COOH$. The *cis* isomer of tiglic acid.
Properties: Colorless needles or prismatic crystals; spicy odor. D 0.9539 (76/4C), mp 45C, bp 185C, refr index 1.4434 (47C). Soluble in alcohol, ether, and hot water.
Derivation: From the root of *Angelica archangelica* or from the oil of *Anthemis nobilis* by distillation.
Use: Flavoring extracts.

angelica oil.
Properties: Essential oil; strong aromatic odor; spicy taste. D 0.853–0.918, optical rotation +16 to +41. Soluble in alcohol. Chief known constituents: phellandrene, valeric acid. Combustible.
Derivation: Distilled from the roots and seeds of *Angelica archangelica* found principally in Europe.
Grade: Technical, FCC.
Use: Preparation of liqueurs, perfumery.

"Angio-Conray" ***[Mallinckrodt].*** TM for an 80% solution of sodium iothalamate used in diagnostic medicine.

angiotensin. (angiotonin; hypertensin). A peptide found in the blood, important in its effect on blood pressure. Both a decapeptide and an octapeptide are known. Their amino acid sequences and hence the complete structures have been established.

angiotonin. See angiotensin.

Ångstrom. (Å). A unit of length almost one one-hundred millionth (10^{-8}) centimeter. The Ångstrom is defined in terms of the wavelength of the red line of cadmium (6438.4696 Å). Used in stating distances between atoms, dimensions of molecules, wavelengths of short-wave radiation, etc.
See nanometer.